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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/829,495	04/09/2001	SAMANTHA J BUSFIELD	MBIO99-057CP4M	8094

7590 01/30/2004

Intellectual Property Group
Millennium Pharmaceuticals, Inc.
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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 01/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/829,495	GILL ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/24/03; 4/9/01*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 August 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8/1/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 43-66 are pending and are being acted upon in this Office Action.

2. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: It does not include the inventors Samantha J Busfield, Jean-Luc Villeval, Martine Jandrot-Perrus, William Vainchencker and Gillian Kingsbury's signature.

3. The disclosure is objected to because of the following informality: "09/345,**0**68" page 3, line 5 should have been 09/345,468. Appropriate action is required.

4. Applicant should amend the first line of the specification to update the relationship between the instant application and 09/345,468, filed 6/30/99, which is now Pat No. 6,245,527 and 09/454,824, filed 12/6/99, which is now abandon.

5. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: Glycoprotein VI antibodies and uses thereof.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 43-66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an antibody or antigen-binding fragment thereof which immunospecifically binds to a TANGO268 antigen comprising SEQ ID NO: 3, wherein the antibody or antigen-binding fragment thereof comprises the variable heavy (VH) chain complementarity determining regions (VHCDR1, VHCDR2 and VHCDR3) and the variable light (VL) chain complementarity determining regions (VLCDR1,VLCDR2 and VLCDR3) comprising

the following sequences: VHCDRI: SEQ ID NO:61; VHCDR2: SEQ ID NO:62; VHCDR3: SEQ ID NO:63; VLCDR1: SEQ ID NO:64; VLCDR2: SEQ ID NO:65; and VLCDR3: SEQ ID NO:66, (2) the said antibody or antigen-binding fragment thereof wherein the antibody is a monoclonal antibody, a human antibody, a humanized antibody, Fab fragment, F(ab')2 fragment or scFv, (3) a conjugated antibody or anti- antigen-binding fragment thereof which immunospecifically binds to a TANGO268 antigen comprising SEQ ID NO: 3, wherein the antibody or antigen-binding fragment thereof comprises the variable heavy (VH) chain complementarity determining regions (VHCDR1, VHCDR2 and VHCDR3) and the variable light (VL) chain complementarity determining regions (VLCDR1,VLCDR2 and VLCDR3) comprising the following sequences: VHCDRI: SEQ ID NO:61; VHCDR2: SEQ ID NO:62; VHCDR3: SEQ ID NO:63; VLCDR1: SEQ ID NO:64; VLCDR2: SEQ ID NO:65; and VLCDR3: SEQ ID NO:66 wherein the antibody is conjugated to a therapeutic or drug moiety, or detectable substance, (4) The said conjugated antibody or binding fragment thereof wherein the detectable substance is selected from the group consisting of an enzyme, a prosthetic group, a fluorescent label, a luminescent label, a biocheminescent label, and a radioactive label, (5) a kit comprising said antibody or binding fragment thereof and instructions for use, (6) a composition comprising the antibody or binding fragment thereof mentioned above and a pharmaceutically acceptable carrier for detection and diagnostic assays, **does not** reasonably provide enablement for (1) *any* antibody or antigen-binding fragment thereof which immunologically binds to any TANGO268 antigen comprises *any* combination of at least one variable heavy (VH) chain complementarity determining region and *any* one variable light (VL) chain complementarity determining region as set forth in claims 43-53, (2) pharmaceutical comprising any antibody or antigen-binding fragment thereof which immunologically binds to any TANGO268 antigen as set forth in claims as set forth in claims 54 and 66 for treating any disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient

to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only antibody or antigen-binding fragment thereof which immunospecifically binds to human TANGO268 antigen comprising SEQ ID NO: 3 wherein the antibody or antigen-binding fragment thereof comprises the variable heavy (VH) chain complementarity determining regions (VHCDR1, VHCDR2 and VHCDR3) and the variable light (VL) chain complementarity determining regions (VLCDR1,VLCDR2 and VLCDR3) comprising the following sequences: VHCDRI: SEQ ID NO:61; VHCDR2: SEQ ID NO:62; VHCDR3: SEQ ID NO:63; VLCDR1: SEQ ID NO:64; VLCDR2: SEQ ID NO:65; and VLCDR3: SEQ ID NO:66. The specification further discloses four other scFvs antibodies that comprises the specific variable heavy (VH) chain complementarity determining regions (VHCDR1, VHCDR2 and VHCDR3) and the variable light (VL) chain complementarity determining regions (VLCDR1,VLCDR2 and VLCDR3) as shown in Table 8 on page 108. The specification also discloses monoclonal antibodies produced by the specific hybridoma that binds to human TANGO and labeled antibody and fragment thereof for detection, and diagnostic assays.

The specification does not teach how to make and use *any* antibody and binding fragment thereof that comprises any combination of heavy and light chain CDRS because there is insufficient guidance for the other CDRs in the heavy and light chains in the claimed antibody or antibody fragment thereof that would bind specifically to human TANGO 268, in turn, would be useful for treating any disease. The specification does not reasonably provide enablement for the broader recitation of an antibody or binding fragment thereof comprising an immunoglobulin that does not contain all of the recited CDR1, CDR2, and CDR3 regions of both the heavy and light chain. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to an antibody comprising heavy and light chain variable regions which encompass any number and/or combination of at least one or two CDR1, CDR2 and CDR3 regions encoded by SEQ ID NO: 61-66.

Janeway *et al* teach that the association of different heavy and light chain variable regions forms the antigen binding site (See page 3:21, last paragraph). Without sufficient guidance as to the other CDRs in the claimed antibody or antigen binding fragment thereof, it is not clear that any combination of CDR regions will have the asserted binding specificity to the human TANGO-268 comprising SEQ ID NO: 3 on the surface of platelet. Given the indefinite number of antibody, there is insufficient guidance as to the binding specificity of the claimed antibody,

much less for treating or preventing any disease such as thrombocytopenia, platelet disorder, liver disorders, stroke, ischemia, venous thromboembolisme, coronary diseases, metastatic cancers and embryonic disorders. Further, the term "TANGO268" has no structure without the amino acid sequence or sequence identifier (SEQ ID NO). Finally, given the indefinite number of disease, there is insufficient *in vivo* working example demonstrating that the claimed pharmaceutical composition comprising said antibody or binding fragment thereof is effective for treating disease such as thrombocytopenia, platelet disorder, liver disorders, stroke, ischemia, venous thromboembolisme, coronary diseases, metastatic cancers and embryonic disorders.

Kuby *et al* teach that immunizing a peptide versus a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide.

Abaza *et al* teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the binding specificity of the antibody against the site (See abstract, in particular).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein such antibody that can tolerate change such as conservative substitutions or no substitution, additions or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Given the indefinite number of disease and indefinite number of undisclosed antibody, a person of skill in the art would not know which undisclosed antibody is effective for treating which undisclosed disease.

With regard to a kit comprising said antibody and antigen-fragment thereof, since the binding specificity of the antibody or antigen-binding fragment thereof is not enabled, it follows that a kit comprising said antibody, or antigen-binding fragment thereof is not enabled. For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of

the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

8. Claims 43-66 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* antibody or antigen-binding fragment thereof which immunologically binds to any TANGO268 antigen comprises *any* combination of at least one variable heavy (VH) chain complementarity determining region and *any* one variable light (VL) chain complementarity determining region as set forth in claims 43-53, (2) pharmaceutical comprising any antibody or antigen-binding fragment thereof which immunologically binds to any TANGO268 antigen as set forth in claims as set forth in claims 54 and 66 for treating any disease.

The specification discloses only antibody or antigen-binding fragment thereof which immunospecifically binds to human TANGO268 antigen comprising SEQ ID NO: 3 wherein the antibody or antigen-binding fragment thereof comprises the variable heavy (VH) chain complementarity determining regions (VHCDR1, VHCDR2 and VHCDR3) and the variable light (VL) chain complementarity determining regions (VLCDR1,VLCDR2 and VLCDR3) comprising the following sequences: VHCDR1: SEQ ID NO:61; VHCDR2: SEQ ID NO:62; VHCDR3: SEQ ID NO:63; VLCDR1: SEQ ID NO:64; VLCDR2: SEQ ID NO:65; and VLCDR3: SEQ ID NO:66. The specification further discloses four other scFvs antibodies that comprises the specific variable heavy (VH) chain complementarity determining regions (VHCDR1, VHCDR2 and VHCDR3) and the variable light (VL) chain complementarity determining regions (VLCDR1,VLCDR2 and VLCDR3) as shown in Table 8 on page 108. The specification also discloses monoclonal antibodies produced by the specific hybridoma that binds to human TANGO and labeled antibody and fragment thereof for detection, and diagnostic assays.

With the exception of the specific antibody or antigen binding fragment thereof that binds specifically to human TANGO comprising SEQ ID NO: 3 having the specific combination of variable heavy (VH) chain complementarity determining region and *any* one variable light (VL) chain complementarity determining region as set forth in claim 55, there is insufficient written description about the other undisclosed CDR in the claimed antibody. Further, the specification

discloses only mouse and human TANGO polypeptides. There is inadequate written description about the other TANGO polypeptide to which the antibody binds. Further, "TANGO 268" does not have a structure (such as amino acid sequence), much less function.

With regard to pharmaceutical composition and kit comprising the said antibody or antigen-binding fragment thereof, since the binding specificity and the other undisclosed CDRs of the claimed antibody are not adequately described, the pharmaceutical composition comprising said undisclosed antibody for treating indefinite number of disease is not adequately described. It also follows that the kit comprising said undisclosed antibody or labeled antibody is not adequately described.

Given the lack of a written description of *any* additional representative species of TANGO 268 antigen to which the claimed antibody binds as encompassed by the claims, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claims 43-66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "TANGO268 antigen" in claims 43 and 55 is indefinite and ambiguous because "TANGO268 antigen" is merely a laboratory designation which does not clearly define the polypeptide to which the claimed antibody binds, since different laboratories may use the same laboratory designation s to define completely distinct polypeptide.

The recitation of "The antibody of claim 43" in claim 44 is indefinite because the preamble of base claim 43 recites "An antibody or antigen-binding fragment thereof...". It is suggested that claim 44 be rewritten to "The antibody or antigen-binding fragment thereof of claim 43...antibody". Likewise, the same correction should be done for claims 45-49.

The "antibody is conjugated to a therapeutic or drug moiety" in claim 50 lacks antecedent basis in base claim 43. It is suggested that claim 50 be rewritten to "A conjugated antibody or antigen binding fragment thereof wherein the antibody or antigen binding fragment thereof of claim 43 is conjugated to a therapeutic or drug moiety". Likewise, the same correction should be done for claim 51. It is also suggested that claim 52 be rewritten to "The conjugated antibody or binding fragment thereof of claim 51 wherein the ...material".

With regard to claim 53, "A kit comprising **an** antibody" should have been "A kit comprising **the** antibody". Likewise, the same correction should be done for claim 54, 65 and 66.

The recitation of "The antibody of claim 55" in claim 56 is indefinite because the preamble of base claim 55 recites "An antibody or antigen-binding fragment thereof...". It is suggested that claim 56 be rewritten to "The antibody or antigen-binding fragment thereof of claim 55...antibody". Likewise, the same correction should be done for claims 57-61.

The "antibody is conjugated to a therapeutic or drug moiety" in claim 62 lacks antecedent basis in base claim 43. It is suggested that claim 62 be rewritten to "A conjugated antibody or antigen binding fragment thereof wherein the antibody or antigen binding fragment thereof of claim 55 is conjugated to a therapeutic or drug moiety". Likewise, the same correction should be done for claim 63. It is also suggested that claim 64 be rewritten to "The conjugated antibody or binding fragment thereof of claim 63 wherein the ...radioactive material".

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 43-66 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 132-136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 155, 157, 159, 161-165, 168-169, 171, 173, 175-178, 180-181, 183, 185, 187-189, 191-192, 194, 196, 198-201, 203, 205, 207-208, 210-213, 215-216, 218, 220, 222-224, 226-227, 229, 233-235, 237-238, 240, 242, 245-251, and 256-264 of copending Application No. 09/610,118 and claims 26-29, 33-47, 53-54, 65-79 and 87-90 of 09/503,387.

13. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to antibody or fragment thereof having the specific binding specificity of TANGO antigen that comprises the specific variable heavy (VH) chain complementarity determining regions and the variable light (VL) chain complementarity determining regions of VHCDR1: SEQ ID NO:61; VHCDR2: SEQ ID NO:62; VHCDR3: SEQ ID NO:63; VLCDR1: SEQ ID NO:64; VLCDR2: SEQ ID NO:65; and VLCDR3: SEQ ID NO:66 (species). The issuance of a patent to instant application (species) anticipates the generic antibody that binds to the human TANGO antigen in claims 132-136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 155, 157, 159, 161-165, 168-169, 171, 173, 175-178, 180-181, 183, 185, 187-189, 191-192, 194, 196, 198-201, 203, 205, 207-208, 210-213, 215-216, 218, 220, 222-224, 226-227, 229, 233-235, 237-238, 240, 242, 245-251, and 256-264 (genus) of 09/610,118 as well as the generic antibody that binds to the human TANGO antigen in claims 26-29, 33-47, 53-54, 65-79 and 87-90 of 09/503,387. Further, the antibody of instant application that comprises VHCDR1: SEQ ID NO: 61; VHCDR2: SEQ ID NO:62; VHCDR3: SEQ ID NO:63; VLCDR1: SEQ ID NO:64; VLCDR2: SEQ ID NO:65; and VLCDR3: SEQ ID NO:66 has identical variable heavy (VH) chain complementarity determining regions (VHCDR1, VHCDR2 and VHCDR3) and the variable light (VL) chain complementarity determining regions (VLCDR1,VLCDR2 and VLCDR3) as the scFvs A10 with patent deposit number PTA-2442 in copending Application No. 09/610,118. The issuance of a patent to 09/610,118 and 09/503,387 would include the antibody of instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

16. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The IFW official Fax number is (703) 872-9306.

Phuong N. Huynh, Ph.D.
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January 26, 2004

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